increase reactive oxygen species and directly regulate blood pressure, thereby linking innate immunity, endothelial dysfunction, and hypertension. There are a number of questions to be addressed in future studies, including those concerning basic science (such as why SDMA is elevated in CKD, why elevated ADMA, also seen in CKD, does not cause the same dysfunction, and how TLR2 signaling proceeds in the absence of TLR1 and/or TLR6), as well as those related to the clinical implications. For example, it is well established that atherosclerosis begins early in life and, to date, all of the risk factors in adults modulate the progression of the disease in the teenage years (McGill et al., 2000). It is also known that the earlier in life risk factor reduction is achieved, the greater the decrease in life-long risk of CVD disease (e.g., Cohen et al., 2006). With this in mind, finding SDMA-modified HDL in children with CKD raises the question that if further clinical studies support SDMA and the associated pathway as important therapeutic targets, how early in life should one begin to avoid paying the toll?

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ILC1 Populations Join the Border Patrol

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It has been unclear whether an innate lymphoid cell (ILC) counterpart to the T helper 1 cell type exists. New studies, including Fuchs et al. (2013) in this issue of *Immunity*, identify T-bet$^+$IFN-γ^+ ILC1 that accumulate in the inflamed intestine of IBD patients.

A burgeoning body of recent literature has described a variety of innate lymphoid cell (ILC) populations arising from a common lymphoid progenitor, that lack rearranged antigen receptors and do not express myeloid or dendritic cell markers (Spits and Cupedo, 2012). ILCs are found at mucosal sites, such as the gastrointestinal tract and lung, where they respond to tissue stress or infection by secreting cytokines that promote innate immunity and tissue repair, but which may also contribute to immunopathology (Spits and Cupedo, 2012). ILC subpopulations are heterogeneous and have been classified according to their expression of key transcription factors and effector cytokines, which mirror the polarization of different CD4$^+$ T helper subsets (Spits et al., 2013; Spits and Cupedo, 2012). Thus, ILC populations that express GATA-3 and secrete T helper 2 (Th2) cell related cytokines are termed ILC2, whereas ILCs that express RORγt and secrete Th17 or Th22 cell related cytokines are termed ILC3 (Spits et al., 2013). Until now, conventional natural killer (NK) cells were regarded as the innate cell Th1 doppelganger. However, three recent studies (Bernink et al., 2013; Fuchs et al., 2013; Klose et al., 2013), including one in this issue of *Immunity* (Fuchs et al., 2013), have identified mucosal Th1 cell innate counterparts in humans and mice. Termed ILC1, these populations express the transcription factor T-bet and release IFN-γ in response to cytokines such as interleukin-12 (IL-12), IL-15, and IL-18.

The search for novel human ILC populations was initially conducted on tonsil samples. Within the CD56$^+$CD3$^-$ cell fraction, Fuchs et al. (2013) identified two distinct populations (NKp44$^+$CD103$^+$ ILC and NKp44$^-$CD103$^-$ ILC) that had the capacity to secrete high amounts of IFN-γ, CCL4, and TNF-α in response to the cytokines IL-12 and IL-15. Consistent with their Th1-like profile, the ILC1 subsets expressed higher amounts of T-bet and lower amounts of RORγt and

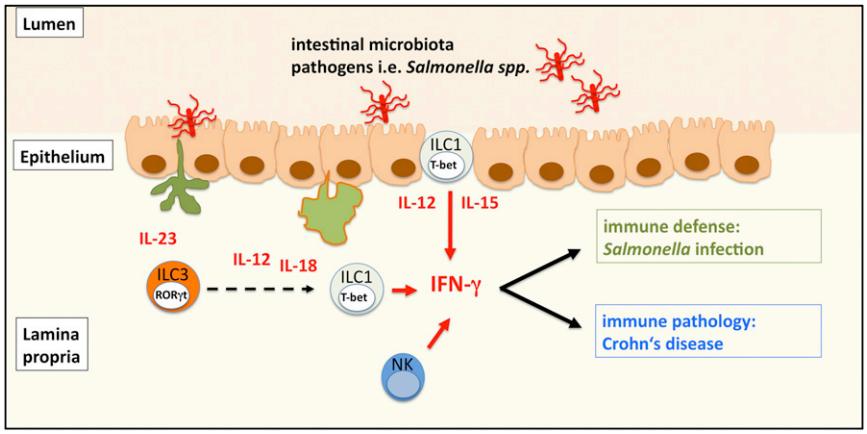

Figure 1. ILC1 Populations Contribute to Protection and Pathology in the Intestine
Subsets of T-bet$^+$IFN-γ$^+$ ILC1 in the murine intestine include intraepithelial ILC1 that respond to IL-12 and IL-15, lamina propria ILC1 that respond to IL-12 and IL-18, and NK cells. RORγt$^+$ ILC3 may switch toward T-bet$^+$ ILC1 cells in response to environmental factors, such as IL-12. ILC1-derived Th1 cytokines may activate protective innate immunity but may also contribute to intestinal pathology.

AHR than ILC3. Independently, Bernink et al. (2013) identified a population of c-Kit$^-$NKp44$^-$ ILC that had similarities to Th1 cells, including high expression of IFN-γ, T-bet, CXCR3, and CCL3. These ILC1 secreted IFN-γ in response to IL-12 and IL-18 and were phenotypically and developmentally distinct from conventional NK cells.

Both studies subsequently demonstrated that human ILC1 were also present in the intestine. The association between Th1-cell cytokine responses and intestinal pathology in Crohn's disease (CD) prompted evaluation of ILC1 cells in CD lesions. Bernink et al. (2013) observed that the intestinal lamina propria (LP) of CD patients contained substantially higher frequencies of c-Kit$^-$NKp44$^-$ ILC1 compared to noninflamed controls. Furthermore, adoptive transfer of human fetal hematopoietic stem cells (HSC) into transgenic mice lacking lymphocytes, NK cells, and ILCs, demonstrated that human ILC could reconstitute the intestinal ILC compartment in mice. Subsequent induction of intestinal inflammation by treatment with dextran sodium sulfate was again accompanied by a dramatic increase in accumulation of c-Kit$^-$NKp44$^-$ ILC1 in the inflamed colon.

In contrast to the lamina propria ILC populations, Fuchs et al. (2013) demonstrated that the NKp44$^+$CD103$^+$ ILC1 subset resided within the epithelial layer of tonsil and intestine, suggesting that, like intraepithelial (IEL) T cells, they may respond to stress or infection of the intestinal epithelium. Indeed, the NKp44$^+$CD103$^+$ ILC1 subset expressed additional IEL surface markers and secreted IFN-γ following coculture with a TLR2-stimulated intestinal epithelial cell (IEC) line, although the signals involved were not identified. Although NKp44$^+$CD103$^+$ ILC1 constituted only a small fraction of IEL found in healthy intestine, there was a dramatic increase in their abundance in inflamed ileal samples taken from CD patients. Murine counterparts of human intraepithelial ILC1 were identified as CD160$^+$NKp46$^+$NK1.1$^+$ ILC that also produced IFN-γ in response to stimulation with IL-12 and IL-15 (Fuchs et al., 2013). In a model of innate immune-mediated colitis, induced by administration of agonistic CD40 mAbs to *Rag1*$^{-/-}$ mice, intraepithelial ILC1 in the small bowel rapidly secreted IFN-γ, and antibody-mediated depletion of NK1.1$^+$ cells led to reduced colitis. Together with previous studies, this suggests that ILC are the key source of pathogenic IFN-γ in this model (Buonocore et al., 2010; Uhlig et al., 2006; Vonarbourg et al., 2010).

Together, these findings indicate that at least two subsets of human ILC1 accumulate in the inflamed intestine in Crohn's disease patients; a CD56$^+$ NKp44$^+$CD103$^+$ ILC1 subset that resides in the epithelium and responds to IL-12 and IL-15 and a CD56$^-$c-Kit$^-$NKp44$^-$ ILC1 subset in the lamina propria that responds to IL-12 and IL-18 (Figure 1). Although the functional contribution of ILC1 to pathology remains to be determined, IFN-γ production is postulated to be a key inflammatory mediator. However, to date, clinical trials of IFN-γ blockade in Crohn's disease have reported only limited beneficial effects; therefore, the therapeutic utility of targeting IFN-γ remains to be demonstrated (Reinisch et al., 2010). It will be important to examine whether ILC1 populations are associated with other intestinal immune disorders. For example, the IL-15 responsive intraepithelial ILC1 subset could potentially be involved in celiac disease, where IEL lymphocytosis is a hallmark of this Th1-cell and IL-15 driven immunopathology (Abadie et al., 2011).

The parallels between ILC and CD4$^+$ Th cell subsets have stimulated investigation of their differentiation pathways and plasticity. Indeed, Bernink et al. (2013) demonstrated that c-Kit$^+$NKp44$^-$RORγt$^+$ ILCs could give rise to either ILC1 or to ILC3 depending on the cytokine environment. Furthermore, c-Kit$^-$NKp44$^-$ ILC1 cells could be derived from NKp44$^+$RORγt$^+$ ILC3 cells following culture with IL-12 and IL-2. Thus, ILC1 can differentiate from other ILC populations, including ILC3, in response to environmental cytokines like IL-12 (Figure 1).

Further clues to the potential differentiation pathways and functions of ILC1 were provided by Klose et al. (2013), who reported that the mouse small intestinal LP harbored a population of CCR6$^-$RORγt$^+$T-bet$^+$ ILC that readily produced IFN-γ and TNF-α, but expressed little IL-22, similar to ILC1. These CCR6$^-$RORγt$^+$T-bet$^+$ ILC differentiated from CCR6$^-$RORγt$^+$ ILC in response to environmental stimuli, such as commensal microbiota, through increased expression of T-bet, which in turn promoted expression of IFN-γ and NKp46. During experimental *Salmonella typhimurium* infection, NKp46$^+$RORγt$^+$T-bet$^+$ ILC mediated early innate IFN-γ secretion that helped maintain the secretion of barrier-protective mucus. Conversely, the enterocolitis induced by *S. typhiumurium* infection was attenuated in mice lacking NKp46$^+$RORγt$^+$IFN-γ$^+$ ILCs, again suggesting that activation of ILC1 cells could contribute to intestinal pathology. Future studies should further define the role of ILC1 in early protective immunity

against intracellular infections in which IFN-γ plays a key protective role. Moreover, the early IFN-γ responses to which ILC1 contribute might sensitize antigen-presenting cells and shape the local microenvironment to influence subsequent effector T cell responses.

These findings extend the diversity of human ILC subsets by describing unique subsets of ILC1 cells that secrete IFN-γ, which may impact protection and pathology in the gut. In addition, the flexible expression of key transcription factors exhibited by ILCs suggests that functional plasticity is an intrinsic property utilized by both innate and adaptive lymphocytes to respond to distinct types of pathogens.

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